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09/444,388	11/22/1999	TAKASHI HIBINO	P21-9042	8598

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/444,388	Applicant(s) Hibino et al
	Examiner Jehanne Souaya	Art Unit 1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Aug 13, 2001 .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 6-16 is/are pending in the application.

4a) Of the above, claim(s) 6 and 7 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 8-16 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Currently, claims 6-16 are pending in the instant application. Claims 6-7 are withdrawn from consideration as being directed to non-elected subject matter. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are newly applied (necessitated by amendment). They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Written Description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method for identifying a breeding marker for polymorphic plants by a) selecting two sibling individual of a plant having different phenotypes, b) obtaining genomic DNA from the individuals, c)isolated and selecting DNA fragments by a genome subtraction method using the genomic DNA from the individuals, d) providing an RNA derived labeled probe wherein the probe is a labeled cDNA of at least one mRNA obtained from the individuals and the cDNA is selected and amplified by oligonucleotide primers in a polymerase chain reaction wherein the primers are designed to hybridize to the mRNA for a plant gene related to the breeding marker, e)fractionating the DNA fragments and screening the DNA fragments with the RNA derived labeled probe, and f) detecting the binding between the DNA fragments and the RNA derived labeled probe. The specification teaches a general method of digesting plant DNA to form DNA fragments, subjecting the DNA fragments to genome subtraction to obtain polymorphic fragments, and screening the polymorphic DNA fragments for a desired DNA fragment (see p 3). More specifically, the specification teaches that the RDA method was used as the genome subtraction method (see p. 8, line 31). The specification teaches that two siblings, *Acacia auricaliformis,* were seeded at the same time and allowed to grow. After 2 years, a difference in 50 cm was found in tree height and a 2 cm difference was found in root diameter (see sentence bridging pp 8 and 9). The specification teaches using genomic DNA prepared from each leaf in a method of genome subtraction where total RNA was extracted (p. 9,

line 5), and a DNA fragment obtained after subtraction was fractionated by acrylamide gel electrophoresis (p. 9, lines 29-32). The specification teaches that positive DNA fragments were subcloned and analyzed. The specification teaches that 6 DNA fragments were obtained (see p. 10, lines 20-22, and FIG 1). The specification teaches that FIG 1 shows the results of genome subtraction and hybridization by an expression probe for acacia, and that the circles indicate DNA fragments selected by subtraction that were judged to be complementary with the experimental probe (see p. 11, lines 1-2). The specification, however, does not teach such a process for obtaining *any* DNA fragment from a plant or the nucleic acid sequence of this DNA fragment. Each of the claimed inventions is a genus for which a representative number of species must be disclosed to meet the written description requirement of 112/1st paragraph. As set forth by the Court in *Vas Cath In. V. Mahurkar,* 19, USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. The specification only teaches a general method of obtaining DNA fragments from plants using genome subtraction. The specification teaches obtaining fragments from *Acacia auriculiformis*, but does not teach if these fragments were in any way related to the difference in height and root diameter observed between the two plants. Furthermore, the specification only shows a gel with bands corresponding to DNA fragments, but does not teach the sequence of such DNA fragments. The specification has only taught a broad method, and the successful isolation of DNA fragments, but has not taught whether these fragments were the "desired" fragments as encompassed by the claimed invention. Absent such a

written description, the specification fails to show that applicant was in fact "in possession of the broadly claimed invention at the time the application for patent was filed.

Response to Arguments

The response traverses the rejection. Initially, the examiner would like to call attention to the fact the 112/1st paragraph rejection made above and in the previous office action were made based on a lack of Written Description, not enablement. The response states that the specification teaches the RDA method for genome subtraction of DNA from two sibling plants of Acacia auricaliformis. The response further states that the specification teaches that FIG 1 shows the results of genome subtraction and hybridization by an expression probe for acacia and that circles indicate DNA fragments selected by subtraction that were judged to be complementary with the experimental probe. This argument has been thoroughly reviewed but was not found persuasive. Firstly, the specification teaches a general method of digesting plant DNA to form DNA fragments, subjecting the DNA fragments to genome subtraction to obtain polymorphic fragments, and screening the polymorphic DNA fragments for a desired DNA fragment. Secondly, while the specification teaches obtaining fragments from *Acacia auricaliformis*, the specification does not teach if these fragments were in any way related to the difference in height and root diameter observed between the two plants. Furthermore, the specification only shows a gel with bands corresponding to DNA fragments, but does not teach the sequence of such DNA fragments. The method taught by the specification is not sufficiently described such that the

skilled artisan could perform the experiments in the specification and predictably and reproducibly obtain the exact nucleic acid fragments of Figure 1. Figure 1 is merely a gel showing DNA fragments that result from a genome subtraction method and hybridization by an expression probe for acacia, and does not provide enough information to allow reproduction of the experiment. The skilled artisan would have no way of knowing if the DNA fragments obtained with the disclosed primers had the same sequence as the fragment in Figure 1 because the specification has not provided enough information to allow a meaningful comparison.

Indefinite

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear whether claim 11 includes a misspelling. The species Acacia auric**a**liformis is not taught in the art, however the species Acacia auric**u**liformis, therefore it is unclear whether the claims should be drawn to Acacia auric**a**liformis or auric**u**liformis.

Claim Rejections - 35 USC § 102

7. Claims 8, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Phillips et al (Plant Molecular Biology, vol. 24, pp 603-615, 1994).

Phillips teaches a subtraction cloning scheme for Arabidopsis thaliana, which resulted in the isolation of differentially regulated cDNA (see abstract). The method of Phillips involves isolating total mRNA from plant material (p. 604), followed by subtractive hybridization using excess 'driver' poly(A)+ RNA form control treated plants with first strand cDNA from GA treated plants to generate polls of either GA induced or Ga repressed sequences (see p. 605, co. 1). Phillips teaches that clones representing mRNA changed in abundance by GA were selected from enriched libraries by differential hybridization (see p. 607, col. 1 "Identification of GA-regulated clones). Phillips teaches that the probes for differential hybridization were generated form single stranded cDNA (p. 607, co. 1). Phillips teaches that the single stranded cDNA remaining after subtraction was converted to double stranded DNA by primer extension and amplified by PCR and that agarose gel electrophoresis revealed that the size range of PCR products was 100 -600 base pairs (p. 608, col 2, first full para). Phillips teaches that differential hybridization of duplicate dot blots of 600 random clones from the enriched cDNA libraries with labeled probes derived from mRNA from GA-treated and control shoots (claim 16) identified only 3-5% strongly hybridizing clones, demonstrating the successful subtraction of abundant DNA species. Phillips teaches that the technique was used to identify two genes whose corresponding mRNA accumulate 24 h after application of GA3 to plants of the Arabidopsis thaliana GA-deficient dwarf mutant ga1 (p. 613, col. 1, "Discussion").

Response to Arguments

The response traverses that the Phillips teaches genes for Arabidopsis thaliana and that the claims involve acacia or acacia auricaliformis plant genes. This argument has been thoroughly reviewed but was found unpersuasive as the method of claim 8 is not drawn to acacia or acacia auricaliformis.

8. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Phillips, in view of Pinyopusarerk, K (ACIAR proceedings, 1987, no. 16, pp 147-148).

Phillips teaches a subtraction cloning scheme for Arabidopsis thaliana, which resulted in the isolation of differentially regulated cDNA (see abstract). The method of Phillips involves isolating total mRNA from plant material (p. 604), followed by subtractive hybridization using excess 'driver' poly(A)+ RNA form control treated plants with first strand cDNA from GA treated plants to generate polls of either GA induced or Ga repressed sequences (see p. 605, co. 1). Phillips teaches that clones representing mRNA changed in abundance by GA were selected from enriched libraries by differential hybridization (see p. 607, col. 1 "Identification of GA-regulated clones). Phillips teaches that the probes for differential hybridization were generated form single stranded cDNA (p. 607, co. 1). Phillips teaches that the single stranded cDNA remaining after subtraction was converted to double stranded DNA by primer extension and amplified by PCR and that agarose gel electrophoresis revealed that the size range of PCR products was 100 -600 base pairs (p. 608, col 2, first full para). Phillips teaches that differential

hybridization of duplicate dot blots of 600 random clones from the enriched cDNA libraries with labeled probes derived from mRNA from GA-treated and control shoots identified only 3-5% strongly hybridizing clones, demonstrating the successful subtraction of abundant DNA species. Phillips teaches that the technique was used to identify two genes whose corresponding mRNA accumulate 24 h after application of GA3 to plants of the Arabidopsis thaliana GA-deficient dwarf mutant ga1 (p. 613, col. 1, "Discussion").

Although Phillips does not teach a plant that is a forest tree and specifically acacia auricaliformis, Pinyopusarerk teaches that the Royal Forest Department of Thailand revised the species of acacia auriculiformis to be used in its reforestation program and that subsequently tree improvement programs have been planed for the species (see p. 147, col. 1). Pinyopusarerk teaches that the improvement program was started with some specific objectives including 1) improve qualities of the species (eg. stem form) through selection and breeding and 2) produce genetically improved seed and other plant material for plantation establishment. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to identify a breeding marker for ie: stem form for acacia auriculiformis, using the methods taught by Phillips as Phillips teaches the successful identification of genes with a specific phenotype. The ordinary artisan would have been motivated to use the method of Phillips to identify a breeding marker for stem form for acacia auriculiformis as Pinyopusarerk teaches a need for improving the quality of the species. It would have been obvious to the

ordinary artisan at the time the invention that identifying such a marker in a specific tree would aid in selection and breeding as taught by Pinyopusarerk.

9. Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Phillips in view of Wigler et al (US Patent 5,436,142) and Nainan et al (J. Of Virological Methods, 1996, vol. 61, pp 127-134).

Phillips teaches a subtraction cloning scheme for Arabidopsis thaliana, which resulted in the isolation of differentially regulated cDNA (see abstract). The method of Phillips involves isolating total mRNA from plant material (p. 604), followed by subtractive hybridization using excess 'driver' poly(A)+ RNA form control treated plants with first strand cDNA from GA treated plants to generate polls of either GA induced or Ga repressed sequences (see p. 605, co. 1). Phillips teaches that clones representing mRNA changed in abundance by GA were selected from enriched libraries by differential hybridization (see p. 607, col. 1 "Identification of GA-regulated clones). Phillips teaches that the probes for differential hybridization were generated form single stranded cDNA (p. 607, co. 1). Phillips teaches that the single stranded cDNA remaining after subtraction was converted to double stranded DNA by primer extension and amplified by PCR and that agarose gel electrophoresis revealed that the size range of PCR products was 100 -600 base pairs (p. 608, col 2, first full para). Phillips teaches that differential hybridization of duplicate dot blots of 600 random clones from the enriched cDNA libraries with labeled probes derived from mRNA from GA-treated and control shoots identified only 3-5%

strongly hybridizing clones, demonstrating the successful subtraction of abundant DNA species. Phillips teaches that the technique was used to identify two genes whose corresponding mRNA accumulate 24 h after application of GA3 to plants of the Arabidopsis thaliana GA-deficient dwarf mutant ga1 (p. 613, col. 1, "Discussion").

Although Philips does not explicitly teach a genome subtraction method that is representation difference analysis (RDA), Wigler teaches methods for representational different analysis (RDA) between two sources of DNA (see col. 2, lines 28-30). Wigler teaches that the method involves the isolation of DNA, where the DNA can be from any source, including plants (see col. 3, lines 47-51). Wigler teaches that in the first stage, DNA is isolated and digested to produce fragments (col. 3, lines 61-65). Wigler teaches that subtractive and kinetic steps are employed in the next stage, in a single operation of hybridization and amplification, which, after several rounds, produces enrichment of target DNA (col. 4, lines 29-65). Wigler teaches that resulting DNA can be used as probes to identify sites which differ (col.5). Wigler teaches that such analysis can be used to define sequences which are present in one member of a family and not in another (see col. 6, lines 1-15). In example 2, Wigler specifically teaches analysis of DNA from two individuals resulting in the detection of a small number of differences between two nearly identical genomes. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the RDA method of Wigler in the genomic subtraction method of Phillips as Wigler specifically teaches analysis of DNA from two individuals resulting in the detection of a small number of differences between two nearly

identical genomes. The ordinary artisan would have been motivated made to use the RDA method of Wigler in the genomic subtraction method of Phillips for the purposes of greater sensitivity when genomes are very similar.

Although Phillips does not teach labeling cDNA with digoxigenin, Nainan teaches a simple system to detect PCR products that has the sensitivity and specificity of nested PCR primer PCR which involves digoxigenin labeled PCR products which can be identified with antidigoxigenin antibodies. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to label the cDNA of the method of Phillips with digoxigenin for the purposes of specifically detecting the cDNA. The ordinary artisan would have been motivated to label the cDNA taught by Phillips with digoxigenin as Nainan teaches that it provides sensitivity and specificity.

Phillips does not teach using the oligonucleotide primers of SEQ ID NOS 1 and 2, however these sequences represent adaptor sequences with restriction sites. Therefore, it would have been prima facie obvious to one of ordinary skill in the art to use adaptor oligonucleotides with restriction sites for the purposes of digesting the fragments prior to fractionation on a gel as is common in RDA methods. Such adaptors are considered functional equivalents in a genome subtraction method, absent secondary considerations.

Conclusion

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1655
Nov. 30, 2001

W. Gary Jones
Supervisory Patent Examiner
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